BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

Eur päisches Patentamt
Eur pean Patent Office
Office européen des brevets

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

01109853.0

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

DEN HAAG, DEN
THE HAGUE, 14/12/01
LA HAYE, LE

Europäisches Patentamt | European Patent Office | Office eur péen des brevets

Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.: 01109853.0
Demande n°:

Anmeldetag:
Date of filing: 23/04/01
Date de dépôt:

Anmelder:
Applicant(s):
Demandeur(s):
F. HOFFMANN-LA ROCHE AG
4070 Basel
SWITZERLAND

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
The use of NK-1 receptor antagonists for the treatment of benign prostatic hyperplasia

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat: State: Pays:	Tag: Date: Date:	Aktenzeichen: File no. Numéro de dépôt:

Internationale Patentklassifikation:
International Patent classification:
Classification internationale des brevets:
/

Am Anmeldetag benannte Vertragstaaten:
Contracting states designated at date of filing: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE/TR
Etats contractants désignés lors du depôt:

Bemerkungen:
Remarks:
Remarques:

F. Hoffmann-La Roche AG, CH-4070 Basle, Switzerland

Case 20876

The use of NK-1 receptor antagonists for the treatment of benign prostatic hyperplasia

The present invention concerns NK-1 receptor antagonists and their use for the treatment and/or prevention of benign prostatic hyperplasia (BPH).

Benign prostatic hyperplasia (BPH) is quite common in older men. Its symptoms may interfere with daily activities and impact the perception of wellbeing and thus the quality of life. BPH can be progressive and lead to urinary retention, infections, bladder calculi and renal failure. While moderate symptoms may remain untreated, bothersome symptoms and complications may need medical therapy or surgery.

Catheterization may be needed in case of an acute urinary retention, one of the complications caused by BPH. There are two different forms of acute urinary retention, viz. spontaneous or precipitated acute urinary retention, whereby the first one is often considered by patients to be the most serious outcome of BPH. Spontaneous acute urinary retention can be treated with 5-alpha-reductase inhibitors, such as finasteride as described by Andersen et al., Urology, 49(6), 839-845, (1997). Precipitated acute urinary retention is an episode of acute urinary retention which often occurs within the first three days after anesthesia or surgery, after a stroke or a congestive heart failure; a medical condition such as prostatitis or urinary tract infection; or ingestion of medication or drugs known to precipitate retention, e.g., pseudoephedrine hydrochloride, cold medicine, pain medication such as narcotics or sedatives, or benadryl.

Benign prostatic hyperplasia (BPH) is unusual in that it occurs spontaneously as a clinical disease in males of only two species, humans and dogs (Emberton M. and Mundy A.R. (1999), "The Prostate and Benign Prostatic Hyperplasia", in The Scientific Basis of Urology, editors Mundy, Fitzpatrick, Neal & George; Isis Medical Media, Oxford UK. 257pp.). Anatomical similarities between canine and human prostate were first extensively reviewed by Price D. in "Comparative aspects of development and structure in the

prostate". Natl. Cancer Inst. Monogr., 12, 1-7, (1963), through developmental studies: the canine prostate surrounds the neck of the bladder and proximal urethra, grossly resembling the human prostate, is of mixed stromal and glandular morphology and is ensheathed in a capsule of smooth muscle, fibrovascular tissue, nerves and ganglia. In BPH of dogs and in men, the epithelial and stromal prostatic elements both increase in amount in a seemingly uncoordinated fashion (see Strandberg J.D. in "Comparative Pathology of Benign Prostatic Hyperplasia", in, Prostatic Diseases, editor Lepor H., W.B. Saunders Company, Philadelphia (2000)). Accordingly, dogs have been used extensively in experimental studies of the etiology, pathogenesis and treatment of BPH (Walsh P.C. and Wilson J.D., "The induction of prostatic hypertrophy in the dog with androstanediol", J. Clin. Invest., 57, 1093-7, (1976); Suzuki K., Okazaki H., Ono Y., Kurokawa K., Suzuki T., Onuma E., Takanashi H., Mamiya Y. and Yamanaka H., "Effect of dual inhibition of 5-a-reductase and aromatase on spontaneously developed canine prostatic hypertrophy", Prostate (NY), 37(2), 70-76, (1998); for a review see also Strandberg J.D. (2000; cited above).

Neurokinin-1 (NK-1) or substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being so-named because of their prompt contractile action on extravascular smooth muscle tissue. The receptor for neurokinin-1 or substance P is a member of the superfamily of G protein-coupled receptors and is named NK-1 receptor. This receptor is widely distributed throughout the mammalian nervous system (especially brain and spinal ganglia) and is also present in the circulatory system and in peripheral tissues (especially the duodenum, the jejunum and the genito-urinary tract). The receptor is believed to be involved in the regulation of a number of diverse biological processes as outlined below.

The central and peripheral actions of the mammalian tachykinin substance P have been associated with numerous inflammatory conditions including migraine, rheumatoid arthritis, asthma, and inflammatory bowel disease as well as mediation of the emetic reflex and the modulation of central nervous system (CNS) disorders such as Parkinson's disease (Neurosci. Res., 7, 187-214, (1996)), anxiety (Can. J. Phys., 75, 612-621, (1997)) and depression (Science, 281, 1640-1645, (1998)).

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and

ocular inflammatory diseases reviewed in "Tachykinin Receptor and Tachykinin Receptor Antagonists", J. Auton. Pharmacol., 13, 23-93, (1993).

Furthermore, neurokinin-1 receptor antagonists are being developed for the treatment of a number of physiological disorders associated with an excess or imbalance of tachykinin, in particular substance P. Examples of conditions in which substance P has been implicated include disorders of the central nervous system such as anxiety, depression and psychosis (International Patent Application, Publication Nos. WO 95/16679, WO 95/18124 and WO 95/23798).

The neurokinin-1 receptor antagonists are further believed to be useful for the treatment of motion sickness and for treatment induced vomiting.

The reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist is described in The New England Journal of Medicine, Vol. 340, No. 3, 190-195, (1999).

Furthermore, US Patent No. 5,972,938 describes a method for treating a psychoimmunologic or a psychosomatic disorder by administration of a tachykinin receptor, such as the NK-1 receptor antagonist.

The usefulness of neurokinin 1 receptor antagonists for the treatment of certain forms of urinary incontinence is furthermore described in Neuropeptides, 32(1), 1-49, (1998) and Eur. J. Pharmacol., 383(3), 297-303, (1999).

NK-1 receptor antagonists have been reported to have also a beneficial effect in the therapy of traumatic brain injury (oral disclosure by Prof. Nimmo at the International Tachykinin Conference 2000 in La Grande Motte, France, October 17-20, 2000 with the title "Neurokinin 1 (NK-1) Receptor Antagonists Improve the Neurological Outcome Following Traumatic Brain Injury", Authors: Nimmo A.J., Bennett C.J., Hu X., Cernak I., Vink R.).

The use of NK-1 receptor antagonists for the treatment or prevention of chronic nonbacterial prostatitis and prostatodynia has been described in International Patent Publication No. WO 99/59583.

International Patent Publication No. WO 01/01922 describes the use of substance P antagonists in the treatment of the adenocarcinomas, particularly genito-urinary tract neoplasms such as prostatic carcinoma.

It has now been found that surprisingly antagonists of the neurokinin 1 (NK-1, substance P) receptor can be used in the treatment and/or prevention of benign prostatic hyperplasia.

The present invention therefore relates to the use of an NK-1 receptor antagonist for the treatment or prevention of benign prostatic hyperplasia.

The present invention also relates to the use of an NK-1 receptor antagonist for the manufacture of a medicament for the treatment and/or prevention of benign prostatic hyperplasia.

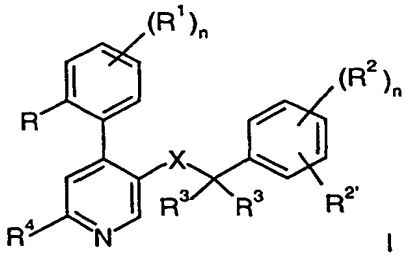
The invention also relates to a method of treating or preventing benign prostatic hyperplasia in a mammal, including a human, by administering an effective amount of an NK-1 receptor antagonist.

The invention also relates to a pharmaceutical composition comprising one or more NK-1 receptor antagonists and a pharmaceutically acceptable excipient for the treatment and/or prevention of benign prostatic hyperplasia. Said NK-1 receptor antagonist may be present in the form of a pharmaceutically acceptable acid addition salt or may be present in the form of a prodrug, preferably in the form of an N-oxide.

The terms "NK-1 receptor antagonist" and "Substance P receptor antagonist" are used herein refer to any synthetic chemical compound that inhibits binding of substance P to the NK-1 receptor. A large number of such receptor antagonists are known and have been described as follows:

- European Patent Publication No. EP-A-1,035,115 of Boes M., Branca Q., Galley G., Godel T., Hoffmann T., Hunkeler W., Schnider P., Stadler H., entitled "Preparation of N-benzyl-4-tolylnicotinamides and related compounds as neurokinin-1 receptor antagonists.". This document as well as all documents referred to below are herewith incorporated by reference in their entirety.

This patent application also describes the preferred NK-1 receptor antagonist of the present invention, viz. compounds of the general formula



I

wherein

R is hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl;

R^1 is hydrogen or halogen; or

R and R^1 may be together –CH=CH-CH=CH-;

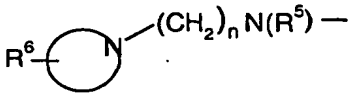
R^2 and $R^{2'}$ are independently from each other hydrogen, halogen, trifluoromethyl, lower alkoxy or cyano; or

R^2 and $R^{2'}$ may be together –CH=CH-CH=CH-, optionally substituted by one or two substituents selected from lower alkyl or lower alkoxy;

R^3 is hydrogen, lower alkyl or form a cycloalkyl group;

R^4 is hydrogen, $-N(R^5)_2$, $-N(R^5)(CH_2)_nOH$, $-N(R^5)S(O)_2$-lower alkyl, $-N(R^5)S(O)_2$-phenyl, $-N=CH-N(R^5)_2$, $-N(R^5)C(O)R^5$ or a cyclic tertiary amine of the group

or the group



;

R^5 is, independently from each other, hydrogen, C_{3-6}-cycloalkyl, benzyl or lower alkyl;

R^6 is hydrogen, hydroxy, lower alkyl, $-(CH_2)_nCOO$-lower alkyl, $-N(R^5)CO$-lower alkyl, hydroxy-lower alkyl, cyano, $-(CH_2)_nO(CH_2)_nOH$, -CHO or a 5-or 6 membered heterocyclic group, optionally bonded via an alkylene group,

X is $-C(O)N(R^5)-$, $-(CH_2)_mO-$, $-(CH_2)_mN(R^5)-$, $-N(R^5)C(O)-$, or $-N(R^5)(CH_2)_m-$;

n is 0 - 4; and

m is 1 or 2;

and the pharmaceutically acceptable acid addition salts and the prodrugs thereof.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination. As used herein, the term "lower alkyl" denotes a straight- or branched-chain alkyl group containing from 1-7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl,

i-butyl, t-butyl and the like. Preferred lower alkyl groups are groups with 1-4 carbon atoms.

The term "lower alkoxy" denotes a group wherein the alkyl residues are as defined above, and which is attached via an oxygen atom.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "cycloalkyl" denotes a saturated carbocyclic group, containing 3-6 carbon atoms.

The term "cyclic tertiary amine" denotes, for example, pyrrol-1-yl, imidazol-1-yl, piperidin-1-yl, piperazin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, 1-oxo-thiomorpholin-4-yl or 1,1-dioxo-thiomorpholin-4-yl.

The term "5 or 6 membered heterocyclic group" denotes, for example pyridinyl, pyrimidinyl, oxadiazolyl, triazolyl, tetrazolyl, thiazolyl, thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, piperazinyl or piperidyl.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulfonic acid, p-toluenesulfonic acid and the like.

Preferred compounds for the claimed use are the exemplary compounds in which X in general formula (I) is $-C(O)N(R^5)-$ and wherein R^5 is methyl, ethyl or cyclopropyl, for example the following compounds:

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-chloro-phenyl)-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-trifluoromethyl-phenyl)-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-fluoro-phenyl)-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-methoxy-phenyl)-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-phenyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-ethyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-cyclopropyl-4-o-tolyl-nicotinamide,
N-[1-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Di-fluorobenzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Di-chlorobenzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-methyl-piperazin-1-yl)-4-o-

tolyl-nicotinamide,
2'-Methyl-5-(4-methyl-piperazin-1-yl)-biphenyl-2-carboxylic acid-(3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-methyl-piperazin-1-yl)-4-naphthalen-1-yl-nicotinamide,
(4-{5-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazin-1-yl)-acetic acid ethyl ester,
5'-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-propyl-piperazin-1-yl)-4-o-tolyl-nicotinamide,
(RS)-6-[3-(Acetyl-methyl-amino)-pyrrolidin-1-yl]-N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-[methyl-(2-morpholin-4-yl-ethyl)-amino]-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-morpholin-4-yl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-thiomorpholin-4-yl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(1-oxo-1l 4-thiomorpholin-4-yl)-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-(1,1-dioxo-1l 6-thiomorpholin-4-yl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-piperazin-1-yl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-cyanomethyl-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-{4-[2-(2-hydroxy-ethoxy)-ethyl]-piperazin-1-yl}-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-[1,2,4]oxadiazol-3- yl-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-[4-(5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl-methyl)-piperazin-1-yl]-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-formyl-piperazin-1-yl)-N-methyl-4-o -tolyl-nicotinamide; or
N-Methyl-N-(2-methyl-naphthalen-1-yl-methyl)-6-morpholin-4-yl-4-o-tolyl-nicotinamide.

Further preferred compounds for the claimed use are the exemplary compounds in which X in general formula (I) is $-N(R^5)-CO-$ and wherein R^5 is hydrogen or methyl, for example the following compounds:

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl-N-methyl-N-(4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-(4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(4-o-tolyl-pyridin-3-yl)-acetamide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(4-o-tolyl-pyridin-3-yl)-propionamide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-morpholin-4-yl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-{6-[methyl-(2-morpholin-4-yl-ethyl)-amino]-4-o-tolyl-pyridin-3-yl}-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-pyrimidin-2-yl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-dimethylamino-pyridin-3-yl]-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-piperazin-1-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-(4-hydroxy-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl)-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-{6-[(2-hydroxy-ethyl)-methyl-amino]-4-o-tolyl-pyridin-3-yl}-N-methyl-isobutyramide,
(R)-2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(3-hydroxy-pyrrolidin-1-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-

pyridin-3-yl)-acetamide; or
[2-(3,5-Bis-trifluoromethyl-phenyl)-2-methyl-propyl]-[4-(4-fluoro-2-methyl-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-methylamine.

The methods for the preparation of the above-mentioned compounds is described in detail in EP-A-1,035,115. Also provided are values for the affinity of selected compounds to the NK-1 receptor, given as pKi, whereby the pKi value for preferred compounds is in the range of 8.00 to 9.80. EP-A-1,035,115 provides furthermore proposals for suitable formulations of NK-1 receptor antagonists, which are also suitable for the use as claimed in the present patent specification.

Methods for the preparation of additional compounds falling within the scope of general formula (I), which compounds are also suitable for the claimed uses are described in European Patent Application 00115846.8 filed July 24, 2000. Examples of such compounds are:

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-6-[1,2,4]triazol-1-yl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-(2-hydroxy-ethylamino)-N-methyl-4-o-tolyl-nicotinamide,
4-Hydroxy-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(2-Hydroxy-ethoxy)-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
(R)-N-(3,5-Bis-trifluoromethyl-benzyl)-6-(3-hydroxy-pyrrolidin-1-yl)-N-methyl-4-o-tolyl-nicotinamide,
4'-(2-Chloro-phenyl)-4-hydroxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(2-hydroxy-ethylamino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(2,3-dihydro-[1,4]oxazin-4-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
N-(6-Acetylamino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide,
N-[6-(Acetyl-methyl-amino)-4-o-tolyl-pyridin-3-yl]-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide,
Cyclopropanecarboxylic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-amide,
Cyclopropanecarboxylic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-methyl-amide,

2-(3,5-Bis-trifluoromethyl-phenyl)-N-(6-imidazol-1-yl-4-o-tolyl-pyridin-3-yl)-N-methyl-isobutyramide; or
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(2-hydroxy-ethylamino)-pyridin-3-yl]-N-methyl-isobutyramide.

The most preferred compound for the use in accordance with the present invention is 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide (Compound A) disclosed in EP-A-1,035,115.

Preferred prodrugs of the compounds of general formula (I) are N-oxides such as the following exemplary compounds:

4-{5-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-4-oxy-piperazine-1-carboxylic acid tert-butyl ester,
5'-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4'-o-tolyl-1-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester,
(RS)-6-[3-(acetyl-methyl-amino)-1-oxo-pyrrolidin-1-yl]-N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-(4-oxy-morpholin-4-yl)-4-o-tolyl-nicotinamide monohydrate,
N-(3,5-bis-trifluoromethyl-benzyl)-6-(1,1-dioxo-1λ^6-4-oxy-thiomorpholin-4-yl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-bis-trifluoromethyl-benzyl)-6-(4-formyl-1-oxy-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide,
N-methyl-N-(2-methyl-naphthalen-1-yl-methyl)-6-(4-oxy-morpholin-4-yl)-4-o-tolyl-nicotinamide,
N-methyl-6-(4-oxy-morpholin-4-yl)-N-naphthalen-1-yl-methyl-4-o-tolyl-nicotinamide,
N-(2-methoxy-naphthalen-1-yl-methyl)-N-methyl-6-(4-oxy-morpholin-4-yl)-4-o-tolyl-nicotinamide,
N-(2-methoxy-benzyl)-N-methyl-6-(4-oxy-morpholin-4-yl)-4-o-tolyl-nicotinamide,
N-(5-chloro-2-methoxy-benzyl)-N-methyl-6-(4-oxy-morpholin-4-yl)-4-o-tolyl-nicotinamide,
N-(2-chloro-5-methoxy-benzyl)-N-methyl-6-morpholin-4-yl-4-o-tolyl-nicotinamide,
N-methyl-6-(4-oxy-morpholin-4-yl)-N-pentafluorophenylmethyl-4-o-tolyl-nicotinamide,

N-methyl-6-(4-oxy-morpholin-4-yl)-N-naphthalen-2-yl-methyl-4-o-tolyl-nicotinamide,
N-[2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]-N-methyl-6-(4-oxy-morpholin-4-yl)-4-o-tolyl-nicotinamide,
N-(1,4-dimethoxy-naphthalen-2-yl-methyl)-N-methyl-6-(4-oxy-morpholin-4-yl)-4-o-tolyl-nicotinamide,
5'-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4'-o-tolyl-1-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid,
2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-oxy-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(4-oxy-morpholin-4-yl)-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(4-oxy-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-[4'-(2-chloro-phenyl)-1-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl]-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-(6-oxy-dimethylamino-4-o-tolyl-pyridin-3-yl)-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-oxy-dimethylamino-pyridin-3-yl]-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-1-(4-hydroxy-1-oxy-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl)-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-{6-[(2-hydroxy-ethyl)-1-oxy-methyl-amino]-4-o-tolyl-pyridin-3-yl}-N-methyl-isobutyramide,
(R)-2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(3-hydroxy-1-oxy-pyrrolidin-1-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-oxy-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-acetamide,
2-(3,5-dimethoxy-phenyl)-N-methyl-N-[6-(4-oxy-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-acetamide; or
2-(3-fluoro-5-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-oxy-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-acetamide.

Methods for the preparation of the above-mentioned N-oxide prodrugs are described in European Patent Application No. 00115287.5 filed July 14, 2000. The most preferred N-oxide prodrug of general formula (I) for the claimed use is 2-(3,5-bis-

trifluoromethyl-phenyl)-N-methyl-N-[6-(4-oxy-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide (Compound B).

Other suitable NK-1 receptor antagonists are described in the following patent publications:

- International Patent Application, WO 0050398 of Boes M., Galley G., Godel T., Hoffmann T., Hunkeler W., Schnider P., Stadler H., entitled "Preparation of phenyl and pyridinyl derivatives as NK-1 receptor antagonists."

- International Patent Publication No. WO 00/50401 of Boes M., Galley G., Godel T., Hoffmann T., Hunkeler W., Schnider P., Stadler H., entitled "Preparation of 3-phenylpyridines as NK-1 receptor antagonists."

- -International Patent Publication No. WO 00/53572 of Boes M., Galley G., Godel T., Hoffmann T., Hunkeler W., Schnider P., Stadler H., entitled "Preparation of biphenyl derivatives as antagonists of the neurokinin-1 receptor."

- -International Patent Publication No. WO 00/73278 of Boes M., Galley G., Godel T., Hoffmann T., Hunkeler W., Schnider P., Stadler H., entitled "Novel 5-phenyl-pyrimidine derivatives as NK-1 receptor antagonists."

- -International Patent Publication No. WO 00/73279 of Boes M., Galley G., Godel T., Hoffmann T., Hunkeler W., Schnider P., Stadler H., entitled "Novel 4-phenyl-pyrimidine derivatives as NK-1 receptor antagonists."

Further preferred NK-1 receptor antagonists useful in connection with the present invention are the following NK-1 receptor antagonists currently under drug development:

GR205171: 3-Piperidinamine, N-[[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]phenyl]methyl]-2-phenyl-, (2S-cis)- (Gardner et al. Regul. Pep. 65:45, 1996)

HSP-117: 3-Piperidinamine, N-[[2,3-dihydro-5-(1-methylethyl)-7-benzofuranyl]methyl]-2-phenyl-, dihydrochloride, (2S-cis)-

L 703,606: 1-Azabicyclo[2.2.2]octan-3-amine, 2-(diphenylmethyl)-N-[(2-iodophenyl)methyl]-, (2S-cis)-, oxalate (Cascieri et al., Mol. Pharmacol. 42, 458, 1992)

L 668,169: L-Phenylalanine, N-[2-[3-[[N-[2-(3-amino-2-oxo-1-pyrrolidinyl)-4-methyl-1-oxopentyl]-L-methionyl-L-glutaminyl-D-tryptophyl-N-methyl-L-phenylalanyl]amino]-2-oxo-1-pyrrolidinyl]-4-methyl-1-oxopentyl]-L-methionyl-L-glutaminyl-D-tryptophyl-N-methyl-, cyclic (8->1)-peptide, [3R-[1[S*[R*(S*)]],3R*]]-

LY 303241: 1-Piperazineacetamide, N-[2-[acetyl[(2-methoxyphenyl)methyl]amino]-1-(1H-indol-3-yl-methyl)ethyl]-4-phenyl-, (R)-

LY 306740: 1-Piperazineacetamide, N-[2-[acetyl[(2-methoxyphenyl)methyl]amino]-1-(1H-indol-3-yl-methyl)ethyl]-4-cyclohexyl-, (R)-

MK-869: 3H-1,2,4-Triazol-3-one, 5-[[2-[1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-, [2R-[2α(R*),3 α]]-

R-544: Ac-Thr-D-Trp(FOR)-Phe-N-MeBzl

Spantide III: L-Norleucinamide, N6-(3-pyridinylcarbonyl)-D-lysyl-L-prolyl-3-(3-pyridinyl)-L-alanyl-L-prolyl-3,4-dichloro-D-phenylalanyl-L-asparaginyl-D-tryptophyl-L-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-leucyl-

WIN-62,577: 1H-Benzimidazo[2,1-b]cyclopenta[5,6]naphtho[1,2-g]quinazolin-1-ol, 1-ethynyl-2,3,3a,3b,4,5,15,15a,15b,16,17,17a-dodecahydro-15a,17a-dimethyl-, (1R,3aS,3bR,15aR,15bS,17aS)-

GR 103,537

L 758,298: Phosphonic acid, [3-[[2-[1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]-, [2R-[2α (R*),3α]]-

NKP608: (2R,4S)-N-[1-{3,5-bis(trifluormethyl)-benzoyl}-2-(4-chloro-benzyl)-4-piperidinyl]-quinoline-4-carboxamide

CGP49823: (2R, 4S)-2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[(4-quinolinyl)methyl]-4-piperineamine) dihydrochloride

CP-96,345: 2S, 3S)-cis-(2(diphenylmethyl)-N-[(2-methoxyphenyl)methyl]-1-azabicyclo[2.2.2]octan-3-amine (Srider et al., Science 251:435, 1991)

CP-99,994: ((2S, 3S)-cis-3-(2-methoxybenzylamino)-2-phenyl-piperidine)dihydrochloride (Desai et al., J. Med. Chem. 35:4911, 1992)

CP-122,721: (+)-2S, 3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine

FK 888: (N2-[(4R)-4-hydroxy-1(1-methyl-1H-indol-3-yl)cabonyl-L-propyl\-N-methyl-N-phenylmethyl-L-3-(2-naphthyl)-alaninamide (Fujii et al., Br. J. Pharm. 107:785, 1992)

GR203040: (2S, 3S and 2R, 3R)-2methoxy-5-tetrazol-1-yl-benzyl-(2-phenyl-piperidin-3-yl)-amine

GR 82334: [D-Pro9,]spiro-gamma-lactam]Leu10, Trp11]physalaemin-(1-11)

GR 94800: PhCO-Ala-Ala-DTrp-Phe-DPe-DPro-Pro-NIe-NH2

L 732,138: N-acetyl-L-tryptophan

L 733,060: ((2S,S)-3-((3, 5-bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl piperidine

L 742,694: (2-(S)-(3. 5-bis(triflurомethyl)benzyloxy)-3-(S)-phenyl-4-(5-(3-oxo-1, 2, 4-triazolo)methylmorpholine

L 754,030: 2-(R)-(1-(R)-3, 5-bis(trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorpholine

LY 303870: (R)-1[N-(2-methoxybenzyl)acetylamino]-3-(1H-indol-3-yl)-2-[N-(2-(4-(piperidinyl)piperidin-1-yl)acetyl)amino]propane

MEN 11149: 2-(2-naphthyl)-1-N-[(1R, 2S)-2-N-[2(H)indol-3-ylcarbonyl]aminocyclohexanecarbonyl]-1-[N'-ethyl-N'-(4methylphenylacetyl)] diaminoethane (Cirillo et al., Eur. J. Pharm. 341:201, 1998)

PD 154075: (2-benzofuran)-CH2OCO]-(R)-alpha-MeTrp-(S)-NHCH(CH3) Ph

RP-67580: (3aR, 7aR)-7, 7-diphenyl-2[1-imino-2(2-methoxyphenyl)-ethyl]+++perhydroisoidol-4-one hydrochloride (Garret et al., PNAS 88:10208, 1991)

RPR 100893: (3aS, 4S, 7aS)-7, 7-diphenyl-4-(2-methoxyphenyl)-2-[(S)-2-(2-methoxyphenyl)proprionyl]perhydroisoindol-4-ol

Spendide: Tyr-D-Phe-Phe-D-His-Leu-Met-NH2

Spantide II: D-NicLys1, 3-PaI3, D-Cl2Phe5, Asn6, D-Trp7.0, NIe11-substance P

SR140333: (S)-1-[2-[3-(3, 4-dichlorphenyl)-1(3-isopropoxyphenylacetyl) piperidin-3-yl] ethyl]-4-phenyl-1 azaniabicyclo [2.2.2]octane (Edmonts et al., Eur. J. Pharm. 250:403, 1993)

WIN-41,708: (17beta-hadroxy-17alpha-ethynyl-5alpha-androstano[3.2-b]pyrimido[1,2-a]benzimidazole

WIN-62,577: 1H-Benzimidazo[2,1-b]cyclopenta[5,6]naphtho[1,2-g]quinazolin-1-ol, 1-ethynyl-2,3,3a,3b,4,5,15,15a,15b,16,17,17a-dodeachydro-15a,17a-dimethyl-,(1R, 3aS, 3bR,15aR, 15bS, 17aS)-

SR-48,968: (S)-N-methyl-N[4-(4-acetylamino-4-[phenylpiperidino)-2-(3,4-dichlorophenyl)-butyl]benzamide

L-659,877: cyclo[Gln, Trp, Phe, Gly, Leu, Met]

MEN 10627: cyclo(Met-Asp-Trp-Phe-Dap-Leu)cyclo(2beta-5beta)

SR 144190: (R)-3(1-[2-(4-benzoyl-2-(3,4-difluorophenyl)-morpholin-2-yl)ethyl]-4-phenylpiperidin-4-yl)-1-dimethylurea

GR 94800: PhCO-Ala-Ala-D-Trp-Phe-D-Pro-Pro-NIe-NH2

SR-142,801: (S)-(N)-(1-(3-(1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl)propyl)-4-phenylpiperidin-4-yl)-N-methyl acetamide

R820: 3-indolylcarbonyl-Hyp-Phg-N(Me)-Bzl

R486: H-Asp-Ser-Phe-Trp-beta-Ala-Leu-Met-NH2

SB 222200: (S)-(-)-N-(a-ethylbenzyl)-3-methyl-2-phenylquinoline-4-carboximide

L 758,298: Phosphonic acid, [3-[[2-[1-[3, 5-bis(trfluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]-2, 5-dihydro-5oxo-1H-1,2,4-triazol-1-yl]-, [2R-[2a(R*), 3a]]-

NK-608: (2R,4S)-N-[1-{3, 5-bis(trifluormethyl)-benzoyl}-2-(4-chloro-benzyl)-4-piperidinyl]-quinoline-4-carboxamide

CGP 47899: Shilling et al., Pers. Med. Chem. 207, 1993

MEN 11467: Evangelista et al., XXIX Nat. Congr. of the Ital. Pharmacological Soc., Florence 20-23.06.1999.

Further information on these NK-1 receptor antagonists under drug development can be found in the published literature.

Additional suitable NK-1 receptor antagonists are described in the following published patents and patent applications.

U.S. Patent No. 5,990,125 in particular the compounds Ia to Ie, X and XVI to XXI, as well as other antagonists comprising quinuclidine, piperidine ethylene diamine, pyrrolidine and azabornane derivatives and related compounds that exhibit activity as substance P receptor antagonists as described in column 33 of USP 5,990,125. These antagonists are preferably used in dosages as specified in column 34 of USP 5,990,125.

Further suitable NK-1 receptor antagonists are described in the following publications:

- U.S. Patent Nos. (USP)

5,977,104	5,162,339	4,481,139	5,232,929
5,998,444	5,242,930	5,373,003	5,981,744
5,387,595	5,459,270	5,494,926	5,496,833
5,637,699			

- Europ. Patent Application, Publ. Nos. (EP-A-)

0 360 390	0 394 989	0 428 434	0 429 366
0 430 771	0 436 334	0 433 132	0 482 539
0 498 069	0 499 313	0 512 901	0 512 902
0 514 273	0 514 274	0 514 275	0 514 276
0 515 681	0 517 589	0 520 555	0 522 808
0 528 495	0 532 456	0 533 280	0 536 817
0 545 478	0 558 156	0 577 394	0 585 913
0 590 152	0 599 538	0 610 793	0 634 402
0 686 629	0 639 489	0 694 535	0 699 655
0 699 674	0 707 006	0 708 101	0 709 375
0 709 376	0 714 891	0 723 959	0 733 632
0 776 893			

- PCT Int. Patent Publ. Nos.(WO)

90/05525	90/05729	91/09844	91/18899
92/01688	92/06079	92/12151	92/15585
92/17449	92/20661	92/20676	92/21677
92/22569	93/00330	93/00331	93/01159
93/01165	93/01169	93/01170	93/06099
93/09116	93/10073	93/14084	93/14113

93/18023	93/19064	93/21155	93/21181
93/23380	93/24465	94/00440	94/01402
94/02461	94/02595	94/03429	94/03445
94/04494	94/04496	94/05625	94/07843
94/08997	94/10165	94/10167	94/10168
94/10170	94/11368	94/13639	94/13663
94/14767	94/15903	94/19320	94/19323
94/20500	94/26735	94/26740	94/29309
95/02595	95/04040	95/04042	95/06645
95/07886	95/08908	95/08549	95/11880
95/14017	95/15311	95/16679	95/17382
95/18124	95/18129	95/19344	95/20575
95/21819	95/22525	95/23798	95/26338
95/28418	95/30674	95/30687	95/33744
96/05181	96/05193	96/05203	96/06094
96/07649	96/10562	96/16939	96/18643
96/20197	96/21661	69/29304	96/29317
96/29326	96/29328	96/31214	96/32385
96/37489	97/01553	97/01554	97/03066
97/08144	97/14671	97/17362	97/18206
97/19084	97/19942	97/21702	97/49710

- British Patent Publ. Nos. (GB)

2 266 529	2 268 931	2 269 170	2 269 590
2 271 774	2 292 144	2 293 168	2 293 169
2 302 689			

As mentioned above benign prostatic hyperplasia (BPH) or prostate hypertrophy is a disease of males, the incidence of which increases considerably after the fifth decade in the life of human beings. It is still not clear what causes BPH, but it appears that BPH is related to the hormone testosterone and its relationship to other hormones that change during the aging process. The fact that the prostate begins to grow larger is not necessarily a problem. In fact, some men have extremely enlarged prostates but suffer no ill effects. On the other hand, some men have prostates that are only slightly enlarged and they suffer from bothersome urinary symptoms. These symptoms include difficulties in urinating, the need to urinate quite frequently, or awaking during the night to urinate.

In serious cases BPH will either be treated through medical therapy using prescription medications or by surgical treatment to remove tissue that is obstructing the flow of urine. Therapy by prescription medication is preferred because it is non-invasive. A number of prescription medications for the treatment of BPH are known, such as e.g. the gonadotrophin agonist leuprorelin sold inter alia under the tradenames Lupron™ and Lupron Depot™ and the 5-alpha reductase inhibitor finasteride sold under the trademark of Proscar™. The present invention provides a novel class of prescription medication for the treatment of BPH, viz. NK-1 receptor antagonists.

NK-1 receptor antagonist for use in connection with the claimed invention may be administered either alone or in combination with other therapeutic agents and are preferably formulated to a pharmaceutical composition comprising pharmaceutically acceptable carriers or diluents. The pharmaceutical preparations to be used in accordance with this invention can in addition also contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants.

NK-1 receptor antagonists can be formulated in the form of a Self-Emulsifying Drug Delivery Systems (SEDDS), which consist of mixtures of oils and surfactants, ideally isotropic, which sometimes include co-solvents. Such mixtures emulsify under conditions of gentle agitation, similar to those which would be encountered in the gastro intestinal tract. When such a formulation is released into the lumen of the gut, it disperses to form a fine emulsion, so that the drug contained in the emulsion remains in solution in the gut, avoiding the dissolution step which frequently limits the rate of absorption of hydrophobic drugs from the crystalline state. SEDDS lead to improved bioavailability and/or a more consistent temporal profile of absorption from the gut. SEDDS have been described by Pouton C.W., in Advanced Drug Delivery Reviews, 25, (1997), 47-58.

The NK-1 receptor antagonist or the pharmaceutically composition comprising it is preferably administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions. The NK-1 receptor antagonist or the pharmaceutically composition comprising it can also be administered via any other suitable way known to the person skilled in the art.

The dosage can vary within wide limits and can, of course, be fitted to the individual requirements in each particular case. The dosage range for a beneficial effect in mammals depends of course on the activity of the NK-1 receptor antagonist that is used, but is usually in the range of 5 to 1000 mg/kg/d and is preferably between 25 and 100 mg/kg/d.

The pharmaceutical preparations in accordance with this invention can in addition also contain pharmaceutically inert, inorganic or organic excipients suitable for the production of tablets, coated tablets, dragees and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragées and hard gelatine capsules.

Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc.

Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

As indicated in the following example below the inventors have shown that NK-1 receptor antagonists, in particular 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide, have the potential to reduce the size of prostate and can therefore be used in the treatment and/or prevention of benign prostatic hyperplasia. While the following example illustrates the invention it is not meant to limit the scope of the claimed invention in any respect.

EXAMPLE

Summary on a 39-week Toxicity Study in the Dog

In a nine-month study four groups of Beagle dogs (4 animals/gender/group; 5-6 months of age at study start) received oral doses (gavage) of 0 (placebo), 6, 20 and 60 mg/kg/d of 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide (Compound A) as a SEDDS formulation for 39 weeks. The following variables were investigated: clinical signs, body weights, food consumption, ophthalmoscopy before and at the end of the study, electrocardiography, heart rate,

toxicokinetics at different time-points, clinical pathology (hematology, biochemistry, urinalysis) in 3-months intervals, necropsy and tissue preservation, organ weights and histopathology.

Dose-related reduced weights of the prostate gland were measured in males at 60 and 20 mg/kg/d (by 58% and 37% when compared to the control) with an insignificant trend also at 6 mg/kg/d. Microscopic changes were limited to all males at 60 and most at 20 mg/kg/d.

The finding was characterized by a smaller overall cross-sectional area, smaller acinar lumina and flatter epithelium with less eosinophilic cytoplasm, particularly in the center of the prostate. However, mitoses were evident in the peripheral acini. The prostate of low dose males was similar to controls.

It is known that the canine prostate exhibits regional differences in the response of the prostatic epithelium to hormonal influences, the peri-urethral (central) glands being more sensitive to androgen withdrawal than sub-capsular (peripheral) zones, as occurred in this study. Thus the prostatic changes seen are considered to reflect a pharmacological effect of the compound used rather than evidence of toxicity.

Mean absolute organ weights were adjusted to 100 g of the mean terminal body weights => mean relative organ weights.

Mean relative organ weights were compared to the corresponding control => % deviation.

Table I

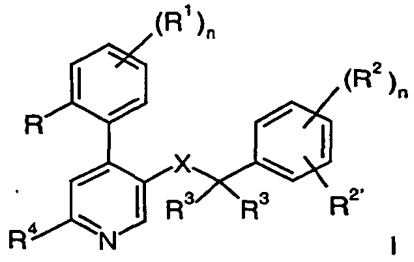
	TESTES			PROSTATE		
Dose		per 100g BW	diff. % vs. control		per 100g BW	diff. % vs. control
mg/kg/d	absolute	relative		absolute	relative	
0/veh	24.006	0.1698	(=100%)	11.006	0.078	(=100%)
6	24.577	0.1803	+ 1%	8.066	0.059	- 24%
20	23.432	0.1804	+ 6%	6.413	0.049	- 37%
60	24.753	0.1853	+ 9%	4.429	0.033	- 58%

Apart from the prostate changes no overt abnormalities in any other organ system was observed. Mild changes in the liver (hepatocyte hypertrophy with slightly increased organ weights) were considered to remain within the normal physiological adaptive range of dogs of this strain, with no signs of an overt systemic effect.

Claims

1. The use of an NK-1 receptor antagonist for the for the manufacture of a medicament for the treatment and/or prevention of benign prostatic hyperplasia.

2. The use according to claim 1, wherein the NK-1 receptor antagonist is a compound of the general formula (I)



I

wherein

R is hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl;

R^1 is hydrogen or halogen; or

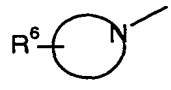
R and R^1 may be together –CH=CH-CH=CH-;

R^2 and $R^{2'}$ are independently from each other hydrogen, halogen, trifluoromethyl, lower alkoxy or cyano; or

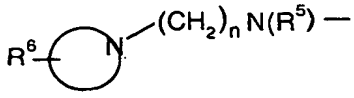
R^2 and $R^{2'}$ may be together –CH=CH-CH=CH-, optionally substituted by one or two substituents selected from lower alkyl or lower alkoxy;

R^3 is hydrogen, lower alkyl or form a cycloalkyl group;

R^4 is hydrogen, $-N(R^5)_2$, $-N(R^5)(CH_2)_nOH$, $-N(R^5)S(O)_2$-lower alkyl, $-N(R^5)S(O)_2$-phenyl, $-N{=}CH-N(R^5)_2$, $-N(R^5)C(O)R^5$ or a cyclic tertiary amine of the group



or the group



;

R^5 is, independently from each other, hydrogen, C_{3-6}-cycloalkyl, benzyl or lower alkyl;

R^6 is hydrogen, hydroxy, lower alkyl, -$(CH_2)_n$COO-lower alkyl, -N(R^5)CO-lower alkyl, hydroxy-lower alkyl, cyano, -$(CH_2)_n$O$(CH_2)_n$OH, -CHO or a 5-or 6 membered heterocyclic group, optionally bonded via an alkylene group,

X is –C(O)N(R^5)-, -$(CH_2)_m$O-, -$(CH_2)_m$N(R^5)-, -N(R^5)C(O)-, or –N(R^5)$(CH_2)_m$-;

n is 0 - 4; and

m is 1 or 2;

and the pharmaceutically acceptable acid addition salts and the prodrugs thereof.

3. The use according to claim 1, wherein the NK-1 receptor antagonist is selected from the following group of compounds, in which X in general formula (I) is –C(O)N(R^5)-, wherein R^5 is methyl, ethyl or cyclopropyl:

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-chloro-phenyl)-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-trifluoromethyl-phenyl)-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-fluoro-phenyl)-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-methoxy-phenyl)-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-phenyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-ethyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-cyclopropyl-4-o-tolyl-nicotinamide,
N-[1-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Di-fluorobenzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Di-chlorobenzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide,
2'-Methyl-5-(4-methyl-piperazin-1-yl)-biphenyl-2-carboxylic acid-(3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-methyl-piperazin-1-yl)-4-naphthalen-1-yl-nicotinamide,
(4-{5-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazin-1-yl)-acetic acid ethyl ester,
5'-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-propyl-piperazin-1-yl)-4-o-tolyl-nicotinamide,

(RS)-6-[3-(Acetyl-methyl-amino)-pyrrolidin-1-yl]-N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-[methyl-(2-morpholin-4-yl-ethyl)-amino]-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-morpholin-4-yl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-thiomorpholin-4-yl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(1-oxo-1l 4-thiomorpholin-4-yl)-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-(1,1-dioxo-1l 6-thiomorpholin-4-yl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-piperazin-1-yl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-cyanomethyl-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-{4-[2-(2-hydroxy-ethoxy)-ethyl]-piperazin-1-yl}-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-[1,2,4]oxadiazol-3- yl-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-[4-(5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl-methyl)-piperazin-1-yl]-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-formyl-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide and
N-Methyl-N-(2-methyl-naphthalen-1-yl-methyl)-6-morpholin-4-yl-4-o-tolyl-nicotinamide.

4. The use according to claim 1, wherein the NK-1 receptor antagonist is selected from the following group of compounds, in which X in general formula (I) is $-N(R^5)-CO-$, wherein R^5 is hydrogen or methyl:

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-N-methyl-isobutyramide,

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl-N-methyl-N-(4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-(4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(4-o-tolyl-pyridin-3-yl)-acetamide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(4-o-tolyl-pyridin-3-yl)-propionamide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-morpholin-4-yl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-{6-[methyl-(2-morpholin-4-yl-ethyl)-amino]-4-o-tolyl-pyridin-3-yl}-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-pyrimidin-2-yl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-dimethylamino-pyridin-3-yl]-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-piperazin-1-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-(4-hydroxy-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl)-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-{6-[(2-hydroxy-ethyl)-methyl-amino]-4-o-tolyl-pyridin-3-yl}-N-methyl-isobutyramide,
(R)-2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(3-hydroxy-pyrrolidin-1-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-acetamide and
[2-(3,5-Bis-trifluoromethyl-phenyl)-2-methyl-propyl]-[4-(4-fluoro-2-methyl-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-methylamine.

5. The use according to claim 1, wherein the NK-1 receptor antagonist is selected from the following group of NK-1 receptor antagonists
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-6-[1,2,4]triazol-1-yl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-(2-hydroxy-ethylamino)-N-methyl-4-o-tolyl-nicotinamide,

4-Hydroxy-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(2-Hydroxy-ethoxy)-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
(R)-N-(3,5-Bis-trifluoromethyl-benzyl)-6-(3-hydroxy-pyrrolidin-1-yl)-N-methyl-4-o-tolyl-nicotinamide,
4'-(2-Chloro-phenyl)-4-hydroxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(2-hydroxy-ethylamino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(2,3-dihydro-[1,4]oxazin-4-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
N-(6-Acetylamino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide,
N-[6-(Acetyl-methyl-amino)-4-o-tolyl-pyridin-3-yl]-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide,
Cyclopropanecarboxylic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-amide,
Cyclopropanecarboxylic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-methyl-amide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-(6-imidazol-1-yl-4-o-tolyl-pyridin-3-yl)-N-methyl-isobutyramide; or
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(2-hydroxy-ethylamino)-pyridin-3-yl]-N-methyl-isobutyramide.

6. The use according to claim 1, wherein the NK-1 receptor antagonist is selected from the following group of NK-1 receptor antagonists
4-{5-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-4-oxy-piperazine-1-carboxylic acid tert-butyl ester,
5'-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4'-o-tolyl-1-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester,
(RS)-6-[3-(acetyl-methyl-amino)-1-oxo-pyrrolidin-1-yl]-N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-(4-oxy-morpholin-4-yl)-4-o-tolyl-nicotinamide monohydrate,
N-(3,5-bis-trifluoromethyl-benzyl)-6-(1,1-dioxo-1λ^6-4-oxy-thiomorpholin-4-yl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-bis-trifluoromethyl-benzyl)-6-(4-formyl-1-oxy-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide,

N-methyl-N-(2-methyl-naphthalen-1-yl-methyl)-6-(4-oxy-morpholin-4-yl)-4-o-tolyl-nicotinamide,
N-methyl-6-(4-oxy-morpholin-4-yl)-N-naphthalen-1-yl-methyl-4-o-tolyl-nicotinamide,
N-(2-methoxy-naphthalen-1-yl-methyl)-N-methyl-6-(4-oxy-morpholin-4-yl)-4-o-tolyl-nicotinamide,
N-(2-methoxy-benzyl)-N-methyl-6-(4-oxy-morpholin-4-yl)-4-o-tolyl-nicotinamide,
N-(5-chloro-2-methoxy-benzyl)-N-methyl-6-(4-oxy-morpholin-4-yl)-4-o-tolyl-nicotinamide,
N-(2-chloro-5-methoxy-benzyl)-N-methyl-6-morpholin-4-yl-4-o-tolyl-nicotinamide,
N-methyl-6-(4-oxy-morpholin-4-yl)-N-pentafluorophenylmethyl-4-o-tolyl-nicotinamide,
N-methyl-6-(4-oxy-morpholin-4-yl)-N-naphthalen-2-yl-methyl-4-o-tolyl-nicotinamide,
N-[2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]-N-methyl-6-(4-oxy-morpholin-4-yl)-4-o-tolyl-nicotinamide,
N-(1,4-dimethoxy-naphthalen-2-yl-methyl)-N-methyl-6-(4-oxy-morpholin-4-yl)-4-o-tolyl-nicotinamide,
5'-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4'-o-tolyl-1-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid,
2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-oxy-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(4-oxy-morpholin-4-yl)-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(4-oxy-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-[4'-(2-chloro-phenyl)-1-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl]-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-(6-oxy-dimethylamino-4-o-tolyl-pyridin-3-yl)-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-oxy-dimethylamino-pyridin-3-yl]-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-1-(4-hydroxy-1-oxy-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl)-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-{6-[(2-hydroxy-ethyl)-1-oxy-methyl-amino]-4-o-tolyl-pyridin-3-yl}-N-methyl-isobutyramide,
(R)-2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(3-hydroxy-1-oxy-pyrrolidin-1-yl)-4-

o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-oxy-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-acetamide,
2-(3,5-dimethoxy-phenyl)-N-methyl-N-[6-(4-oxy-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-acetamide; or
2-(3-fluoro-5-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-oxy-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-acetamide.

7. The use according to claim 1, wherein the NK-1 receptor antagonist is 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide and pharmaceutically acceptable salts thereof.

8. The use according to claim 1, wherein the NK-1 receptor antagonist is 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-oxy-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide and pharmaceutically acceptable salts thereof.

9. The use according to claim 1, wherein the NK-1 receptor antagonist is selected from the group of NK-1 receptor antagonists under drug development designated GR205171, HSP-117, L 703,606, L 668,169, LY 303241, LY 306740, MK-869, R-544, Spantide III, WIN-62,577, GR 103,537, L 758,298, NKP608, CGP49823, CP-96,345, CP-99,994, CP-122,721, FK 888, GR203040, GR 82334, GR 94800, L 732,138, L 733,060, L 742,694, L 754,030, LY 303870, MEN 11149, PD 154075, RP-67580, RPR 100893, Spendide, Spantide II, SR140333, WIN-41,708, WIN-62,577, SR-48,968, L-659,877, MEN 10627, SR 144190, GR 94800, SR-142,801, R820, R486, SB 222200, L 758,298 and NK-608 or a pharmaceutically acceptable salt thereof.

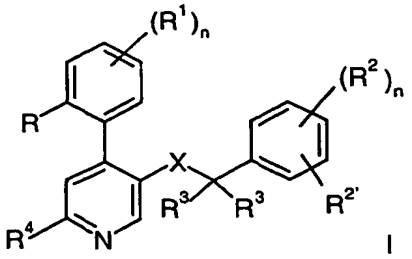
10. A pharmaceutical composition comprising one or more NK-1 receptor antagonists as claimed in any one of claims 1 to 9 and a pharmaceutically acceptable excipient for the treatment and/or prevention of benign prostatic hyperplasia.

11. The invention as herein before described.

***

Abstract

The invention relates to the use of an NK-1 receptor antagonist for the treatment or prevention of benign prostatic hyperplasia (BPH). The preferred NK-1 receptor antagonists are compounds of the general formula



I

wherein

R is hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl;

R^1 is hydrogen or halogen; or

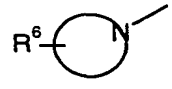
R and R^1 may be together –CH=CH-CH=CH-;

R^2 and $R^{2'}$ are independently from each other hydrogen, halogen, trifluoromethyl, lower alkoxy or cyano; or

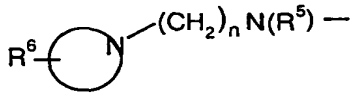
R^2 and $R^{2'}$ may be together –CH=CH-CH=CH-, optionally substituted by one or two substituents selected from lower alkyl or lower alkoxy;

R^3 is hydrogen, lower alkyl or form a cycloalkyl group;

R^4 is hydrogen, $-N(R^5)_2$, $-N(R^5)(CH_2)_nOH$, $-N(R^5)S(O)_2$-lower alkyl, $-N(R^5)S(O)_2$-phenyl, $-N=CH-N(R^5)_2$, $-N(R^5)C(O)R^5$ or a cyclic tertiary amine of the group



or the group



;

R^5 is, independently from each other, hydrogen, C_{3-6}-cycloalkyl, benzyl or lower alkyl;

R^6 is hydrogen, hydroxy, lower alkyl, $-(CH_2)_nCOO$-lower alkyl, $-N(R^5)CO$-lower alkyl, hydroxy-lower alkyl, cyano, $-(CH_2)_nO(CH_2)_nOH$, -CHO or a 5-or 6 membered heterocyclic group, optionally bonded via an alkylene group,

X is $-C(O)N(R^5)-$, $-(CH_2)_mO-$, $-(CH_2)_mN(R^5)-$, $-N(R^5)C(O)-$, or $-N(R^5)(CH_2)_m-$;

n is 0 - 4; and

m is 1 or 2;

and the pharmaceutically acceptable acid addition salts and the prodrugs thereof. The invention also relates to pharmaceutical composition comprising one or more such NK-1 receptor antagonists and a pharmaceutically acceptable excipient for the treatment and/or prevention of benign prostatic hyperplasia.

***